[10] Y. Tobe, T. Fujii, H. Matsumoto, K. Tsumuraya, D. Noguchi, N. Nakagawa, M. Sonoda, K. Naemura, Y. Achiba, T. Wakabayashi, *J. Am. Chem. Soc.* **2000**, *122*, 1762.

[11] Compounds **2a**, **b**, **4a–d**, and **5** were obtained as mixtures of diastereomers, which were not separated, due to orientation of the propellane units. Only one of the isomers is drawn for each of the structures.

[12] Monitoring the reaction with HPLC showed several peaks during the initial stage of the photolysis, which then disappeared after prolonged irradiation, finally leaving only the peak of indan.

[13] The ^{1}H NMR spectrum exhibits an AA′BB′ pattern for the aromatic protons with the same integration value as that of the protons of the propelladiene unit. The ^{13}C NMR spectrum displays two signals for tertiary aromatic carbon atoms and ten signals for sp carbon atoms. The UV/Vis spectrum exhibits a few absorption maxima in the long wavelength region (λ_{max} ($CHCl_3$) 426 (ε 15000), 397 (50000), and 368 (90000) nm) which are reminiscent of those of the diphenyloctatetrayne chromophore (λ_{max} (CH_2Cl_2) 415 (ε 18600), 381 (33400), and 353 (43800) nm: M. M. Haley, M. L. Bell, S. C. Brand, D. B. Kimball, J. J. Pak, W. B. Wan, *Tetrahedron Lett.* **1997**, *38*, 7483). Finally, the mass spectrum exhibits a peak at *m*/*z* 677 [M^++1], which is attributed to the molecular ion of **5**. See Supporting Information for details.

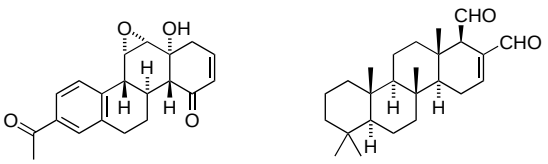
[14] The ΔH_f° values (AM1) for the model compounds of **5** and **6**, in which the propellane units are substituted by cyclobutene, are 660 and 675 kcal mol^{-1} and their bond angles around the sp carbon atoms are 173.1–173.7° and 164.1–170.2°, respectively.

The Zipper-Mode Domino Intramolecular Diels–Alder Reaction: A New 0 →ABCD Strategy for Steroids and Related Compounds**

Marck Nörret and Michael S. Sherburn*

In the push towards more efficient syntheses of organic molecules, processes which lead to a rapid increase in structural complexity are playing an increasingly important role.[1] Multiple bond-forming processes involving parallel transformations (e.g. two-directional synthesis,[2] the generation of libraries of compounds) or sequential transformations[3] (e.g. domino reactions, multiple component couplings) are often utilized to achieve this goal.

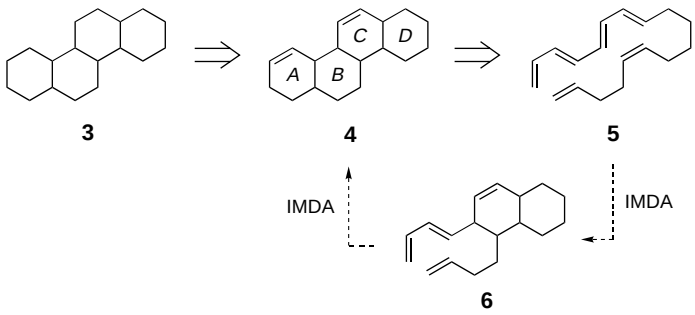
Herein we report an efficient strategy for the one-step stereoselective synthesis of tetracycles of the perhydrochrysene class (i.e. D-homosteroid)—found in many biologically active naturally products such as the nicandrenones (e.g. NIC-10 **1**)[4] and scalarane sesterterpenes (e.g. scalarenedial **2**)[5]—



1 **2**

from a simple and readily prepared acyclic precursor. This unprecedented domino sequence generates four rings, four C–C bonds, and eight contiguous stereocenters in a single operation and, as such, represents a new 0 →ABCD strategy for the synthesis of steroids and related compounds.[6, 7]

The essence of our approach is depicted in Scheme 1. Retrosynthetic introduction of disubstituted alkenes into the A and C rings of saturated tetracycle **3** permits the implementation of two intramolecular Diels–Alder (IMDA) transforms.[8–10] Thus, the tetracyclic diene **4** is retrosynthetically unzipped[11] to furnish simple acyclic precursor **5**, carrying a linearly conjugated tetraene (the bis-diene) tethered to an internal dienophile which, in turn, is tethered to a second, terminal dienophile.



3 **4** **5** **6**

Scheme 1. The domino zipper-mode IMDA reaction of hexaenes **5** to fused tetracycles **4**.

For a successful realization of the synthetic transformation of an acyclic hexaene **5** into a tetracycle such as **4**, a regioselective intramolecular cycloaddition of the more proximate, internal diene-internal dienophile pair must occur first (i.e. **5** →**6**). The bicyclic system thus formed has pendant diene and dienophile "arms" attached to neighboring ring atoms which must come together for the second IMDA reaction to ensue (ie. **6** →**4**). Inspection of molecular models reveals that cycloaddition transition states are readily adoptable for both of the expected diastereomers of bicyclic intermediate **6**.

We were concerned with the potential for generating many stereoisomers of tetracycle **4**. The parent 1,3,9-decatriene, for example, undergoes an unselective IMDA reaction at 250 °C (*cis*:*trans*-fused product ratio = 53:47).[12] Clearly, the judicious incorporation of functionality into unsubstituted system **5** was the key to obtaining stereocontrol in this domino reaction. Thus, we elected to prepare hexaene **12** to test this concept since both dienophile moieties of **12** carry activating groups which were anticipated to lead to facile and stereoselective IMDA reactions.[8]

[*] Dr. M. S. Sherburn, M. Nörret
School of Chemistry
University of Sydney
Sydney, NSW 2006 (Australia)
Fax: (+61) 2-9351-6650
E-mail: M.Sherburn@chem.usyd.edu.au

[**] We thank Dr. Simon Fielder (HortResearch New Zealand) and Mr. Leon Wong (University of Sydney) for preliminary experiments, Dr. Kelvin Picker (University of Sydney) for assistance with HPLC and GC analyses, and Dr. Ian Luck (University of Sydney) for 2D NMR experiments. This work was supported by The Australian Research Council and The University of Sydney.

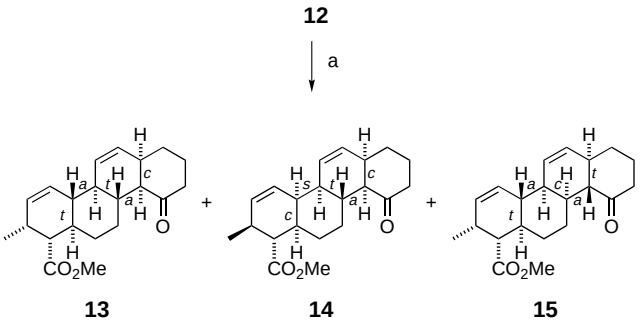
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/01/4021-4074 $ 17.50+.50/0

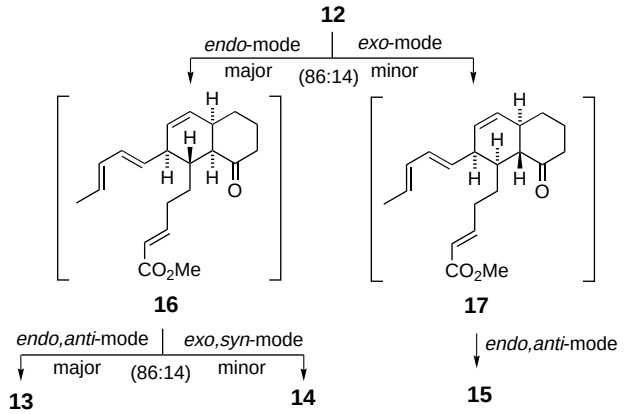
In light of the expected sensitivity of the conjugated tetraene moiety[13] a short, doubly convergent synthetic approach to acyclic hexaene **12** was developed (Scheme 2). Thus, the stabilized ylide **9**, prepared by non-classical Wittig reaction[14] of methylenetriphenylphosphorane with δ-valerolactone,[15] was coupled with aldehyde **10**[16] to give a primary alcohol[17] which was oxidized to aldehyde **11**. The semi-stabilized ylide derived from phosphonium salt **8** was employed as the Wittig coupling partner for **11**. Phosphonium salt **8** was prepared by the addition of vinylmagnesium bromide to 3,5-hexadienal **7** followed by exposure of the resulting trienol[18] to triphenylphosphane hydrobromide. The Wittig reaction between **11** and the ylide derived from **8** is best carried out at low temperatures; under these conditions **12** is formed as an approximate 2:1 (*E*:*Z*) mixture about the newly formed C=C bond. This mixture can be equilibrated to an approximately 5:1 (*E*:*Z*) mixture upon exposure to a sub-stoichiometric amount of iodine in dilute solution.[19]

Cyclization of acyclic precursor **12** was examined under a variety of conditions (PhMe, PhH, CH_2Cl_2 solvents with and without various quantities of Lewis acid promoters from $-78\,^{\circ}C$ to $110\,^{\circ}C$) until optimum conditions were uncovered. After much experimentation, we were delighted to find that hexaene **12** undergoes the novel domino IMDA sequence in 79% yield upon exposure to 1.9 molar equivalents of Et_2AlCl in refluxing CH_2Cl_2 for 30 min (Scheme 3). Three chromatographically separable tetracyclic products **13**, **14**, and **15** are formed under these conditions in a 72:14:14 ratio.[20] The stereochemistry of each of these three double cycloadducts was deduced from 2D NMR experiments (COSY, NOESY, HMBC, and HETCOR) and the stereochemistry of the major product was confirmed by single-crystal X-ray structure analysis.[21] We were unable to observe putative bicyclic intermediates **16** and **17** (Scheme 4) during this reaction, irrespective of the reaction conditions employed. This observation points to the second Diels–Alder reaction (cf. **6**→**4**; Scheme 1) being significantly more facile than the first (cf. **5**→**6**; Scheme 1). We conclude that the conversion of **12**→**13**, **14**, and **15** is a true domino process.[3a]

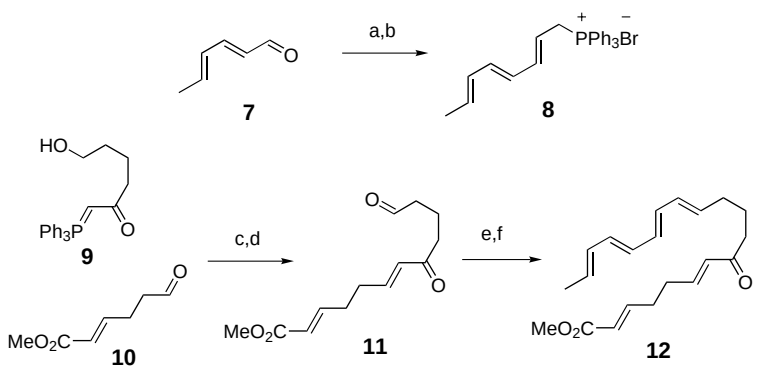
We note that, if both Diels–Alder reactions are concerted [4+2] cycloaddition events (i.e. if diene and dienophile geometry is conserved in the double Diels–Alder reaction), eight diastereomeric tetracyclic products are possible. Clearly, for a complex mixture of stereoisomeric products to be avoided, *both* IMDA events in this domino sequence must be highly stereoselective processes. This is evidently the case for precursor **12** (Scheme 4). The *cis*-fused C/D ring system in products **13** and **14** results from an initial *endo*-docking mode, whereas the *trans*-fused C/D moiety in **15** indicates a minor *exo*-pathway for this first cycloaddition event.[22] Both *cis*- and *trans*-fused monoadducts **16** and **17** undergo highly stereoselective IMDA reactions: of the four stereoisomers which may be formed in each case, **16** gives two[23] and **17** furnishes only one. Moreover, the stereochemistry about the six contiguous stereocenters of the ring junction positions of **13** and **14** mirrors that seen naturally in cholic acids and the cardiac glycosides, respectively.[24]



Scheme 3. The domino IMDA reaction. Reagents and conditions: a) Et_2AlCl (1.9 equiv), CH_2Cl_2, 40 °C, 30 min, 79%; **13**:**14**:**15** = 72:14:14.



Scheme 4. IMDA stereoselectivities en route to the cycloadducts.



Scheme 2. Synthetic route to domino IMDA precursor **12**. Reagents and conditions: a) CH_2=CHMgBr (1.1 equiv), THF, RT, Ar, 4 h, then NH_4Cl/H_2O, 98%; b) $Ph_3P\cdot HBr$, CH_2Cl_2, RT, Ar, 2 h, 92%; c) **9** (1.0 equiv) + **10** (1.0 equiv), CH_2Cl_2, RT, Ar, 48 h, 76%; d) Dess–Martin periodinane (1.8 equiv), CH_2Cl_2, RT, Ar, 48 h, 68%; e) **8** (2.8 equiv) + *n*BuLi (1.9 equiv), THF, $-78\,^{\circ}C$, Ar, 5 min, then **11** (1.0 equiv), $-78\,^{\circ}C$, 2 h, 62%; f) I_2 (0.05 equiv), CH_2Cl_2, RT, Ar, 2 h, 48%.

The work described herein represents a "proof-of-principle" study for the zipper-mode domino IMDA sequence depicted in Scheme 1. This extremely concise approach to tetracycles offers new opportunities for the preparation of steroids and steroid-like compounds. This strategy is particularly attractive for the preparation of biologically (and commercially) important 18- and 19-norsteroids, compounds which are currently prepared through lengthy stepwise synthetic routes.[25] Studies towards this end, involving the use of enantiopure Lewis acid promoters to control the absolute

stereochemistry of the tetracyclic products,[26] are currently under investigation in this laboratory.

Experimental Section

Domino IMDA reaction of **12**: A dry Ar-flushed Schlenk tube was charged with **12** (52.0 mg, 0.158 mmol) and dry, distilled CH_2Cl_2 (7 mL). To the stirred solution at reflux under Ar was added Et_2AlCl (0.301 mmol, 167 μL (1.9 equiv) of a 1.8 M solution in toluene) in one portion. After 30 min at reflux the solution was cooled to ambient temperature, aqueous $NaHCO_3$ (10 mL) was added, and the product was extracted into Et_2O (3×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure to give a yellow oil (48 mg). Flash chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (50:1), afforded **13** ($R_f = 0.46$ in CH_2Cl_2/EtOAc (10:1)) as a white solid (29.8 mg, 0.091 mmol, 57 %) and a mixture of **14** and **15** ($R_f = 0.56$ in CH_2Cl_2/EtOAc (10:1), 11.2 mg). The two minor tetracycles were separated on HPLC (Partisil 10, EtOAc/hexane (8:92), flow rate 3 mL min^{-1}) to give **14** (5.5 mg, 0.017 mmol, 11 %) as a colorless oil and **15** (5.6 mg, 0.017 mmol, 11 %) as a white solid.

Characterization data for **13**: m.p. 109 – 111 °C; ^{1}H NMR (600 MHz, C_6D_6, 25 °C, TMS): $\delta = 5.77$ (d, $J = 10.8$ Hz, 1H; H-11), 5.75 (d, $J = 10.9$ Hz, 1H; H-1), 5.51 (ddd, $J = 10.1$, 4.4, 1.9 Hz, 1H; H-2), 5.48 (ddd, $J = 10.1$, 4.5, 1.5 Hz, 1H; H-12), 3.36 (s, 3H; H-21), 2.62 (dd, $J = 11.6$, 6.2 Hz, 1H; H-4), 2.55 – 2.47 (m, 1H; H-3), 2.38 (dd, $J = 10.1$, 5.6 Hz, 1H; H-14), 2.20 (ddt, $J = 12.7$, 3.2, 3.2 Hz, 1H; H-6α), 2.27 – 2.23 (m, 1H; H-16), 2.09 – 2.04 (m, 1H; H-13), 1.80 (dt, $J = 5.7$, 13.6 Hz, 1H; H-16), 1.60 – 1.49 (m, 2H; H-5, H-17), 1.46 – 1.33 (m, 5H; H-7, H-8, H-9, H-10, H-18), 1.27 – 1.12 (m, 3H; H-7, H-17, H-18), 0.98 (d, $J = 7.1$ Hz, 3H; H-19), 0.78 (dq, $J = 12.7$, 3.7 Hz, 1H; H-6β); ^{13}C NMR (100.6 MHz, C_6D_6, 25 °C, TMS): $\delta = 210.9$ (C=O), 173.3 (COOR), 132.8 (=CH), 131.4 (=CH), 126.9 (=CH), 125.9 (=CH), 56.6 (CH), 50.7 (OCH_3), 50.0 (CH), 46.0 (CH), 45.3 (CH), 39.8 (CH), 39.7 (CH_2), 38.0 (CH), 36.7 (CH), 32.5 (CH), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 18.0 (CH_3); IR (thin film): $\tilde{\nu}_{max} = 3028$, 2924, 2861, 1737, 1704 cm^{-1}; MS (EI, 70 eV): m/z (%): 328 (100) [M^+]; elemental analysis (%) calcd for $C_{21}H_{28}O_3$: C 76.79, H 8.59; found: C 76.87, H 8.69.

Received: June 29, 2001 [Z17389]

[1] P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind. (London)* **1997**, 765 – 769.

[2] a) C. S. Poss, S. L. Schreiber, *Acc. Chem. Res.* **1994**, *27*, 9 – 17; b) S. R. Magnuson, *Tetrahedron* **1995**, *51*, 2167 – 2213.

[3] a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131 – 163; b) *Chem. Rev.* **1996**, *96*, issue 1 (Special issue: Guest editor: P. A. Wender); c) L. F. Tietze, F. Haunert in *Stimulating Concepts in Chemistry* (Eds.: M. Shibasaki, J. F. Stoddart, F. Vögtle), Wiley-VCH, Weinheim, **2000**, p. 39 – 64.

[4] B. M. Stoltz, T. Kano, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9044 – 9045, and references therein.

[5] Recent synthetic efforts: a) E. J. Corey, G. Luo, L. S. Lin, *J. Am. Chem. Soc.* **1997**, *119*, 9927 – 9928; b) E. J. Corey, G. Luo, L. S. Lin, *Angew. Chem.* **1998**, *110*, 1147 – 1149; *Angew. Chem. Int. Ed.* **1998**, *37*, 1126 – 1128; c) A. Abad, C. Agullo, A. C. Cunat, M. C. Llosa, *Chem. Commun.* **1999**, 427 – 428; d) H. Soetjipto, N. Furuichi, T. Hata, S. Katsumura, *Chem. Lett.* **2000**, 1302 – 1303.

[6] Existing 0 → ABCD approaches to steroids and related compounds: a) biomimetic electrophilic polyene cascades: W. S. Johnson, *Angew. Chem.* **1976**, *88*, 33; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9 – 17; b) intramolecular [2+2+2]/Diels-Alder: S. H. Lecher, N. H. Nguyen, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 856 – 858; c) sequential cyclic carbopalladation: Y. Zhang, G. Wu, G. Angel, E. Negishi, *J. Am. Chem. Soc.* **1990**, *112*, 8590 – 8592; d) enynallene cycloaromatization/radical cyclization: Y. W. Andemichael, Y. Huang, K. K. Wang, *J. Org. Chem.* **1993**, *58*, 1651 – 1652; e) annulations of Fischer carbene complexes: J. Bao, W. D. Wulff, V. Dragisich, S. Wenglowsky, R. G. Ball, *J. Am. Chem. Soc.* **1994**, *116*, 7616 – 7630; f) sequential radical cyclizations: H. M. Boehm, S. Handa, G. Pattenden, L. Roberts, A. J. Blake, W.-S. Li, *Perkin 1* **2000**, 3522 – 3538; C. Heinemann, M. Demuth, *J. Am. Chem. Soc.* **1999**, *121*, 4894 – 4895. P. A. Zoretic, H. Fang, A. A. Ribeiro, *J. Org. Chem.* **1998**, *63*, 7213 – 7217, and references therein.

[7] For other efficient approaches to steroids see, for example: a) W. Deng, M. S. Jensen, L. E. Overman, P. V. Rucker, J.-P. Vionnet, *J. Org. Chem.* **1996**, *61*, 6760 – 6761; b) L. F. Tietze, T. Nöbel, M. J. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971 – 8977; c) S. Woo, S. Legoupy, S. Parra, A. G. Fallis, *Org. Lett.* **1999**, *1*, 1013 – 1016; d) M. G. Banwell, D. C. R. Hockless, J. W. Holman, R. W. Longmore, K. J. McRae, H. T. T. Pham, *Synlett* **1999**, 1491 – 1494; e) P.-Y. Michellys, P. Maurin, L. Toupet, H. Pellissier, M. Santelli, *J. Org. Chem.* **2001**, *66*, 115 – 122; f) E. Marsault, A. Toro, P. Nowak, P. Deslongchamps, *Tetrahedron* **2001**, 57, 4243 – 4260, and references therein.

[8] Reviews of the IMDA reaction: a) W. Oppolzer, *Angew. Chem.* **1977**, *89*, 10; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10 – 23; b) D. F. Taber, *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer, Berlin, **1984**; c) A. G. Fallis, *Can. J. Chem.* **1984**, *62*, 183 – 234; d) E. Ciganek, *Org. React.* **1984**, *32*, 1 – 374; e) D. Craig, *Chem. Soc. Rev.* **1987**, *16*, 187 – 238; f) W. R. Roush in *Advances in Cycloaddition*, *Vol. 2* (Ed.: D. P. Curran), JAI, Greenwich, CT, 1990, p. 91 – 146; g) W. R. Roush in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, Oxford, **1991**, p. 513 – 550; h) D. Craig in *Stereoselective Synthesis (Houben-Weyl) 4th ed. 1952 –*, Vol. E21c, **1995**, p. 2872 – 2904.

[9] For a review of tandem Diels – Alder sequences, see J. D. Winkler, *Chem. Rev.* **1996**, *96*, 167 – 176.

[10] A "timed" intermolecular Diels – Alder/intramolecular Diels – Alder sequence on a linear conjugated tetraene has been reported: G. A. Kraus, M. J. Taschner, *J. Am. Chem. Soc.* **1980**, *102*, 1974 – 1977.

[11] Two distinct approaches for constructing fused polycyclic systems from linear acyclic precursors have been identified:[6c] the "crochet" mode[6a,b] and the "zipper" mode.[6c]

[12] M. K. Diederich, F. G. Klarner, B. R. Beno, K. N. Houk, H. Senderowitz, W. C. Still, *J. Am. Chem. Soc.* **1997**, *119*, 10255 – 10259.

[13] H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 103 – 112.

[14] P. J. Murphy, S. E. Lee, *Perkin 1* **1999**, 3049 – 3066.

[15] Alcohol-protected versions of this ylide have been reported: a) P. J. Murphy, H. L. Williams, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron* **1996**, *52*, 8315 – 8332; b) H. J. Bestmann, M. Schmidt, *Tetrahedron Lett.* **1986**, *27*, 1999 – 2000.

[16] H. O. House, T. H. Cronin, *J. Org. Chem.* **1965**, *30*, 1061 – 1070.

[17] All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, and UV/Vis spectroscopy, mass spectrometry, and combustion analyses and/or high-resolution mass spectrometric analysis.

[18] C. W. Spangler, D. A. Little, *J. Chem. Soc. Perkin Trans. 1* **1982**, 2379 – 2385.

[19] This step is not necessary: control experiments in which a mixture of 2*E*, 4*E*, 6*E*, 8*E*- and 2*E*, 4*E*, 6*E*, 8*Z*-undecatetraenes (W. Boland, N. Schroer, C. Sieler, M. Feigel, *Helv. Chim. Acta* **1987**, *70*, 1025 – 1040) was exposed to Et_2AlCl resulted in disappearance of the *Z* isomer. We ascribe this result to $Z \rightarrow E$ isomerization rather than selective decomposition of the 2*E*, 4*E*, 6*E*, 8*Z*-isomer. See reference [23] for a similar observation with a substituted diene.

[20] Other stereoisomers represent < 5 % of the crude product mixture as evidenced by ^{1}H NMR spectroscopic, GC, and HPLC analysis.

[21] P. Turner, M. S. Sherburn, M. Nörret, unpublished results.

[22] A highly *endo*-selective first IMDA reaction is expected based upon literature precedent: W. Oppolzer, R. L. Snowden, D. P. Simmons, *Helv. Chim. Acta* **1981**, *64*, 2002 – 2021.

[23] A related IMDA reaction gave the same stereoisomer under thermal conditions as the sole product: M. Ihara, A. Katsumata, M. Egashira, S. Suzuki, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.* **1995**, *60*, 5560 – 5566.

[24] Cholic acids possess the *cis,anti,trans,anti,trans* (C5-C10-C9-C8-C14-C13) stereochemistry (c.f. **13**), whereas bufadienolides and cardenolides exhibit the *cis,anti,trans,syn,cis* stereochemistry (c.f. **14**): J. R. Hanson, *Nat Prod. Rep.* **2000**, *17*, 423 – 434.

[25] E. J. Corey, A. X. Huang, *J. Am. Chem. Soc.* **1999**, *121*, 710 – 714.

[26] Enantioselective catalysis of IMDA reactions: D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc.* **1999**, *121*, 7559 – 7573.

  1433-7851/01/4021-4076 $ 17.50+.50/0